Novel PAR-1-based Therapeutic Compounds for Neuro-inflammatory Diseases (Tel Hashomer)
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Joav Chapman and Efrat Shavit-Stein, Sheba Medical Center, Israel

Abstract

Many neurological diseases are known to be associated with increased inflammation and over activation of protease activated receptors (PAR) by protein factors of the coagulation cascade. We suggest a coagulation-based protease inhibitor potentially affecting mostly neuronal PAR as a novel intervention site for neurological disease.

Thrombin is a protease well known for its role in coagulation. In addition to its role in the coagulation cascade, thrombin affects many cellular events by a group of receptors named protease activated receptors (PARs) PAR-1 to PAR. PAR-1 has been found in many tissues including the brain where it is found on several cell types including neurons, astrocytes and microglia. PAR-1 is localized to the non-compacted myelin of Schwann cells at the node of Ranvier and in the neuromuscular junction it is localized to the peri-synaptic glia and the post-synaptic muscle. We were the first to show a functional role for PAR-1 activation on the glia component of the node of Ranvier in the PNS where activation of the receptor caused conduction block. PAR-1 activation was shown to hold a physiological role at the CNS synapse where its activation modulates synaptic transmission by causing LTP and seizure-like activity and potentiates the synaptic NMDA receptor. PAR-1 is a marker of glial structures adjacent to the most physiologically active parts of the nervous system, the synapse and the node of Ranvier. Activation of these structures through PAR-1 has profound effects on electophysiology and therefore these glial structures and especially the PAR-1 receptors on them are a novel and highly promising target for therapy in disease.

We have collected many significant findings supporting the role of PAR-1 activation in mediating neurological dysfunction in disease. We have found that thrombin-like activity was elevated in sciatic nerves derived from animal models of both Guillain-Barr&#65533;Syndrome (GBS) (EAN) and diabetic neuropathy (STZ). In both models a significant decreased PAR-1 level was found together with increased physiological thrombin-inhibitors (PN-1, PN-2) indicating that the natural response of the nervous system in these diseases is to increase thrombin inhibition. A relatively general thrombin inhibitor, N alpha-tosyl-L-lysine chloromethyl ketone (TLCK), as well as the PAR-1 antagonist (SCH79797) were found to increase nerve conduction and improve neuropathy associated clinical deficits of these GBS and diabetes model animals significantly.

The Need

Neuropathy is a general term indicating a disease which affects peripheral nerves. The most common cause of neuropathy is diabetes mellitus, occurring in 60% of all

diabetic patients. Diabetic peripheral neuropathy (DPN), one of the most prevalent forms of diabetes-related neuropathy, principally manifests itself as sensory loss and weakness of the lower limbs and ultimately accounts for significant morbidity contributing to amputation. In the PNS the prototypical inflammatory disease affecting nerve cells is the Guillain-Barr syndrome (GBS). GBS is a group of acute inflammatory neuropathies and its animal model is experimental autoimmune neuritis (EAN). Acute inflammatory demyelinating polyneuropathy (AIDP) is the most common form of GBS, and is characterized by demyelination of peripheral axons and axonal degeneration in severe cases. The mechanism leading to GBS are still being elucidated and most of the evidence points to an immune attack at the node of Ranvier.

The Market

GlobalDatas analysis suggests that the global Diabetic Neuropathy(DN) market was worth $ 1.41 billion in 2010. It is forecast to grow at a Compound Annual Growth Rate (CAGR) of 8.5% for the next seven years, to reach $ 2.49 billion by 2017. This is primarily attributed to the increase in the prevalence of the disease and the strong pipeline with new first-in-class therapies.

The global diabetic neuropathy therapeutics market is attractive, with high unmet need. This unmet need in the market is around 41%, which is approximately valued at $ 0.58 billion. The unmet need is due to the lack of availability of effective treatment options targeting disease progression, difficulties in diagnosis and the moderate safety profile of the marketed drugs. The efficacy of the marketed products is moderate. The current treatment options focus on symptomatic relief and are only moderately efficacious. The DN market offers opportunity for newer disease modifying treatment options.

GlobalData analyzed the current competitive landscape for DN drugs and found that the competition is moderate to weak. There are only two FDA (Food and Drug Administration) approved products which are Cymbalta (duloxetine) from Eli Lilly and Lyrica (pregabalin) from Pfizer but these are targeting diabetic neuropathy pain only. In addition, gabapentin and amitriptyline are also used as off label drugs for the treatment of pain associated with diabetic neuropathy. Generics such as topical capsaicin are also used but such products do not hold a major share in the market. The other available drug classes for the treatment of the pain associated with DN are antidepressants, antiepileptics, opioids and NSAIDs (Non-Steroidal Anti-Inflammatory Drug). The competition is weak due to a lack of competing products for Cymbalta and Lyrica. The market has a huge potential for molecules with better safety and efficacy profile and especially such molecules targeting disease progression and offering a cure for DN.

Contact: Sylvie Luria PhD. CEO

Technology Transfer Company

Tel Hashomer Medical Research, Infrastructure and Services Ltd.

Tel: +972-3-5305998 Fax: +972-3-5305944 Cell: 052-6667277

sylvie.luria@sheba.health.gov.il http://research.sheba.co.il/e/